secretion, an effect called *hidromeiosis*.[48] The glands' responsiveness can be at least partly restored if the skin is allowed to dry (eg, by increasing air movement[49]), but prolonged sweating also causes histological changes, including depletion of glycogen, in the sweat glands.[50]

THERMOREGULATORY RESPONSES DURING EXERCISE

Vigorous exercise can increase oxygen consumption and heat production within the body 10-fold or more, depending on the individual's aerobic fitness. Unless exercise is very brief, it is soon accompanied by increases in the heat-dissipating responses—skin blood flow and sweating—to counter the increase in heat production. Although hot environments also elicit heat-dissipating responses, exercise ordinarily accounts for the greatest demands on the thermoregulatory system for heat dissipation, and exercise provides an important example of how the thermoregulatory system responds to a disturbance in heat balance.

Exercise and thermoregulation impose competing demands on the circulatory system. Exercise requires large increases in blood flow to exercising muscle, and the thermoregulatory responses to exercise require increases in skin blood flow. Muscle blood flow is several times as great as skin blood flow during exercise, but the increase in skin blood flow involves disproportionately large demands on the cardiovascular system, as discussed below. Moreover, if the water and electrolytes lost through sweating are not replaced, the resulting reduction in plasma volume will eventually create a further challenge to cardiovascular homeostasis.

Restoration of Heat Balance During Exercise

Exercise increases heat production so that it exceeds heat loss and causes core temperature to rise. The increase in core temperature, in turn, elicits heat-loss responses, but core temperature continues to rise until heat loss has increased enough to match heat production, so that heat balance is restored and core temperature and the heat-loss responses reach new steady state levels. Because the heat-loss responses are proportional to the increase in core temperature, the increase in core temperature at steady state is proportional to the rate of heat production, and thus to the metabolic rate.

A change in ambient temperature changes the levels of sweating and skin blood flow that are needed to maintain any given rate of heat dissipation. However, the change in ambient temperature is accompanied by a skin temperature change that elicits, via both direct and reflex effects, much of the required change in these responses. For any given rate of heat production, there is a range of environmental conditions (sometimes called the "prescriptive zone"; see Chapter 3, Physical Exercise in Hot Climates: Physiology, Performance, and Biomedical Issues) within which ambient temperature changes elicit the necessary changes in heat-dissipating responses almost entirely through the effects of skin temperature changes, with virtually no effect on core temperature at steady state.[51] (The limits of this range of conditions depend on the rate of heat production, and on such individual factors as skin surface area and state of heat acclimatization.) Within this range, core temperature reached during exercise is nearly independent of ambient temperature; and for this reason it was once believed that the increase in core temperature during exercise is caused by an increase in the thermoregulatory set point,[52] just as during fever. As stated previously, however, the increase in core temperature with exercise is an example of a load error rather than an increase in set point. Note the following differences between fever and exercise (Figure 2-12):

- First, although heat production may increase substantially (through shivering) when core temperature is rising early during fever, it does n ot need to stay high to maintain the fever, but in fact returns nearly to prefebrile levels once the fever is established. During exercise, however, an increase in heat production not only causes the elevation in core temperature but is necessary to sustain it.
- Second, while core temperature is rising during fever, rate of heat loss is, if anything, lower than before the fever began; but during exercise, the heat-dissipating responses and the rate of heat loss start to increase early and continue increasing as core temperature rises. (Although in this chapter the term "fever" is used to mean specifically an elevation in core temperature due to pyrogens and occurring in connection with infection or other inflammatory process, some authors use "fever" more loosely to mean any significant elevation of core temperature.)

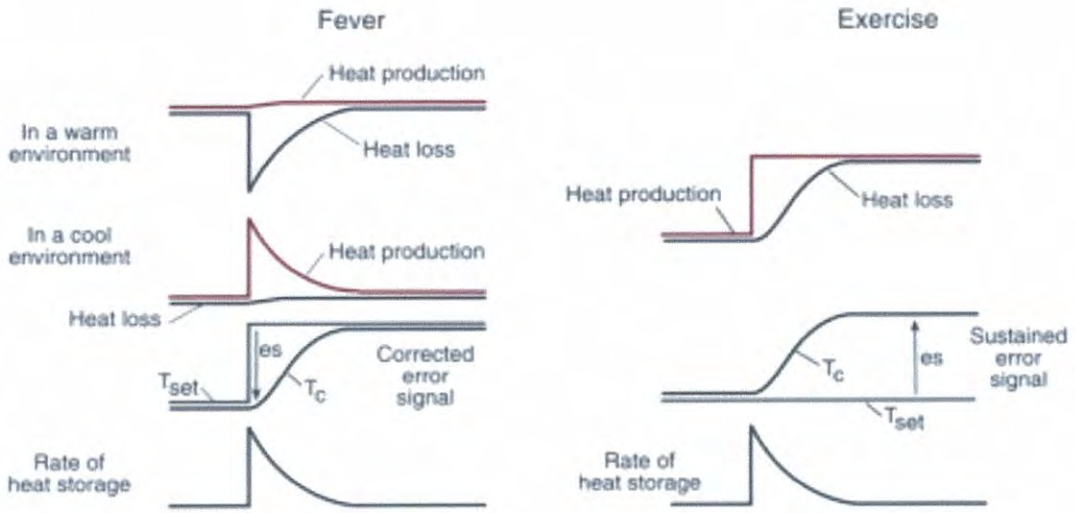

Fig. 2-12. Thermal events during the development of fever (left) and the increase in core temperature (T_c) during exercise (right). The error signal, es, is the difference between T_c and the set point, T_{set}. At the start of a fever, T_{set} has risen, so that T_{set} is higher than T_c, and es is negative. At steady state, T_c has risen to equal the new level of T_{set} and es is corrected (ie, it returns to zero). At the start of exercise, $T_c = T_{set}$ so that es = 0. At steady state, T_{set} has not changed but T_c has increased and is greater than T_{set}, producing a sustained error signal, which is equal to the load error. The error signal (or load error) is here represented with an arrow pointing down for $T_c < T_{set}$, and with an arrow pointing up for $T_c > T_{set}$. Adapted with permission from Stitt JT. Fever versus hyperthermia. *Fed Proc.* 1979;38:43.

Challenge of Exercise in the Heat to Cardiovascular Homeostasis

As pointed out earlier, skin blood flow increases during exercise in order to carry all of the heat that is produced to the skin. In a warm environment, where the temperature difference between core and skin is relatively small, the necessary increase in skin blood flow may be several liters per minute.

Impairment of Cardiac Filling

Whereas the work of supplying the skin blood flow required for thermoregulation in the heat may represent a heavy burden for a patient with cardiovascular disease,[53] in healthy subjects the primary cardiovascular burden of heat stress results from impairment of venous return.[29,30,54] As skin blood flow increases, blood pools in the large, dilated cutaneous vascular bed, thus reducing central blood volume and cardiac filling (Figure 2-13). Because stroke volume is decreased, a higher heart rate is required to maintain cardiac output. These effects are aggravated by a decrease in plasma volume if the large amounts of salt and water lost in the sweat are not replaced. Because the main cation in sweat is sodium, disproportionately much of the body water lost in sweat is at the expense of extracellular fluid, including plasma, although this effect is mitigated if the sweat is dilute.

Compensatory Cardiovascular Responses

Several reflex adjustments help to maintain cardiac filling, cardiac output, and arterial pressure during exercise and heat stress. The cutaneous veins constrict during exercise; and because most of the vascular volume is in the veins, constriction makes the cutaneous vascular bed less compliant and reduces peripheral pooling. Splanchnic and renal blood flow are reduced in proportion to the intensity of the exercise or heat stress. This reduction of blood flow has two effects. First, it allows a corresponding diversion of cardiac output to skin and exercising muscle. Second, because the splanchnic vascular beds are very compliant, a decrease in their blood flow reduces the amount of blood pooled in them[29,30] (see Figure 2-13), helping to compensate for decreases in central blood volume caused by reduced plasma volume and blood pooling in the skin. Because of the essential thermoregulatory function of skin blood flow during exercise and heat stress, the body preferentially compromises splanchnic and renal flow to maintain cardiovascular homeostasis.[55] Above a certain level of cardiovascular strain, however, skin blood flow, too, is compromised.

Despite these compensatory responses, heat stress markedly increases the thermal and cardiovascular strain that exercise produces in subjects

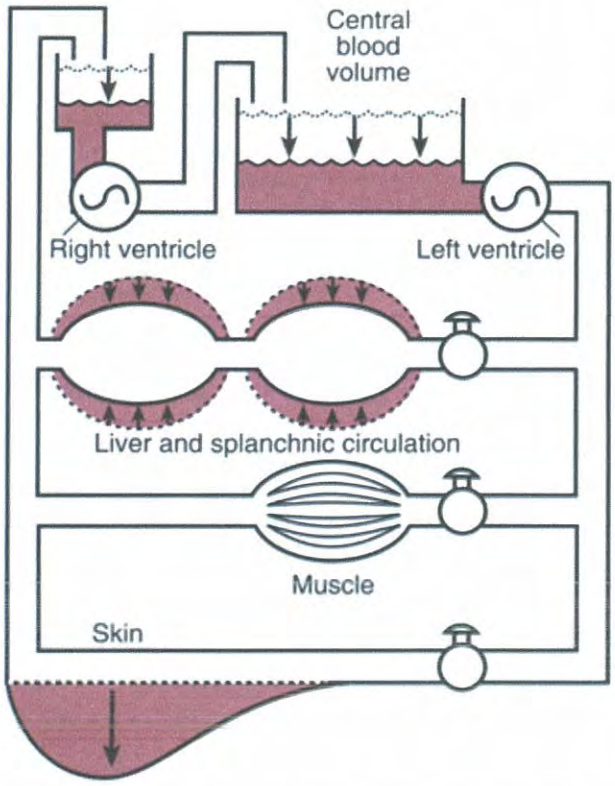

Fig. 2-13. Schematic diagram of the effects of skin vasodilation on peripheral pooling of blood and the thoracic reservoirs from which the ventricles are filled, and also the effects of compensatory vasomotor adjustments in the splanchnic circulation. The valves drawn at the right sides of liver/splanchnic, muscle, and skin vascular beds represent the resistance vessels that control blood flow through those beds. Arrows show the direction of the changes during heat stress. Adapted with permission from Rowell LB. Cardiovascular aspects of human thermoregulation. *Circulation Res*. 1983;52:367–379.

who are unacclimatized to heat. A comparison of responses on the first day of exercise on hot days with those on cool days shows some effects of unaccustomed environmental heat stress on the responses to exercise (Figure 2-14[56]). On the first day in the heat, heart rate during exercise reached a level about 40 beats per minute higher than in the cool environment, to help compensate for the effects of impaired cardiac filling and to maintain cardiac output; and rectal temperature during exercise rose one Centigrade degree higher than in the cool environment. Other effects of exercise–heat stress may include headache, nausea and vomiting secondary to splanchnic vasoconstriction, dizziness, cramps, shortness of breath, dependent edema, and orthostatic hypotension.

During prolonged exercise there is a gradual "drift" in several cardiovascular and thermoregulatory responses. This may include a continuous rise in heart rate, accompanied by a fall in stroke volume and reductions in aortic, pulmonary arterial, and right ventricular end-diastolic pressures.[57] Rowell named these changes "cardiovascular drift," and thought of them as appearing as early as after 15 minutes of exercise.[57] He and Johnson[57,58] empha-

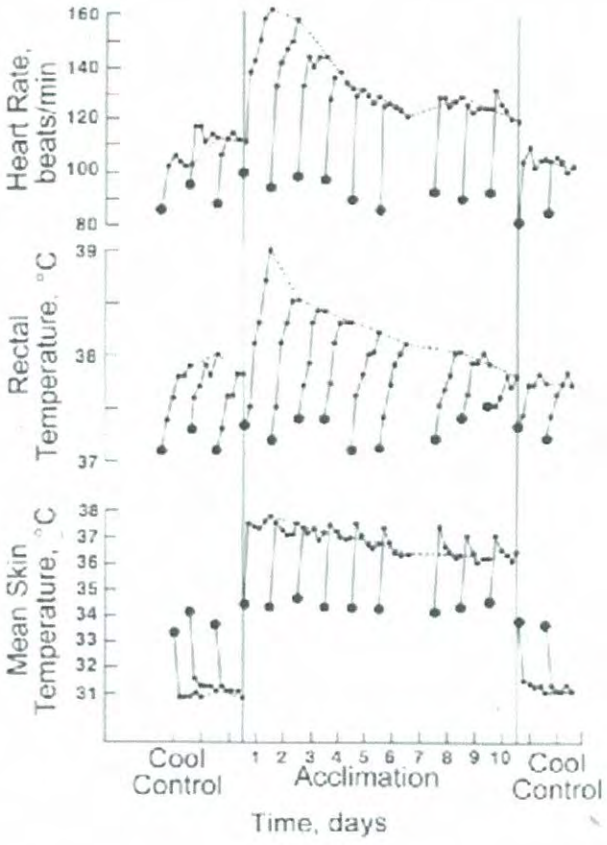

Fig. 2-14. Change in the responses of heart rate, rectal temperature, and mean skin temperature during exercise in a 10-day program of acclimation to dry heat (50.5°C, 15% relative humidity [rh]), together with responses during exercise in a cool environment before and after acclimatization. (The "cool control" conditions were 25.5°C, 39% rh.) Each day's exercise consisted of five 10-minute treadmill walks at 2.5 mph (1.12 m/s) up a 2.5% grade. Successive walks were separated by 2-minute rest periods. Large circles show values before the start of the first exercise period each day, small circles show values at the ends of successive exercise periods, and dotted lines connect final values each day. Adapted with permission from Eichna LW, Park CR, Nelson N, Horvath SM, Palmes ED. Thermal regulation during acclimatization in a hot, dry (desert type) environment. *Am J Physiol*. 1950;163:588.

sized the role of thermoregulatory increases in skin blood flow in producing cardiovascular drift. However, later authors[59–61] have described, as part of the picture of cardiovascular drift, an upward creep in core temperature, which may begin only after a period of apparent thermal steady state (eg, after 30–60 min of exercise). In some of these studies, most but not all of the changes in cardiovascular and thermoregulatory responses could be prevented by replacing fluid lost in sweat, suggesting that these changes were mostly secondary to changes in plasma volume and osmolality due to sweating. Other factors that may affect cardiovascular and thermoregulatory function during prolonged exercise include changes in myocardial function, changes in baroreceptor sensitivity or peripheral α-adrenergic receptor responsiveness (see Tibbits[62] and Raven and Stevens[63] for a discussion of these effects), or an upward adjustment of the thermoregulatory set point,[64] presumably due to some sort of inflammatory response and perhaps elicited by products of muscle injury. These effects have not been investigated extensively, and little is known about the underlying physiological or pathological mechanisms. Some of these effects have been reported only after several hours of exercise or near exhaustion, and little is known about the conditions of exercise duration and intensity required to produce them and their persistence after the end of exercise. Although their functional significance is, as yet, only poorly understood, these changes may be important in limiting performance during prolonged strenuous activity, such as forced marches.

FACTORS THAT ALTER HEAT TOLERANCE

Heat Acclimatization

Prolonged or repeated exposure to stressful environmental conditions elicits significant physiological changes, called *acclimatization*, which reduce the physiological strain that such conditions produce. (The nearly synonymous term, *acclimation*, is often applied to such changes produced in a controlled experimental setting.[12]) Figure 2-14 illustrates the development of these changes during a 10-day program of daily treadmill walks in the heat. Over the 10 days, heart rate during exercise decreased by about 40 beats per minute, and rectal and mean skin temperatures during exercise decreased more than 1°C. Because skin temperature is lower after heat acclimatization than before, dry (nonevaporative) heat loss is less (or, if the environment is warmer than the skin, dry heat gain is greater). To compensate for the changes in dry heat exchange, evaporative heat loss—and thus sweating—increases. The three classic signs of heat acclimatization are

- lower heart rate,
- lower core temperature, and
- higher sweat rate during exercise–heat stress.

Other changes include

- an increased ability to sustain sweat production during prolonged exercise-heat stress, which is essential to increasing tolerance time;
- decreased solute concentrations in sweat;
- redistribution of sweating from trunk to limbs;
- increases in total body water and changes in its distribution;
- metabolic and endocrine changes; and
- other poorly understood changes that protect against heat illness.

The overall effect of heat acclimatization on performance can be quite dramatic, so that acclimatized subjects can easily complete exercise in the heat, which previously was difficult or impossible. Figure 3-22 in Chapter 3, Physical Exercise in Hot Climates: Physiology, Performance, and Biomedical Issues, in this textbook graphically shows the day-to-day improvement in performance during a 7-day program of heat acclimation.

At any given air temperature, increasing the humidity impedes evaporation of sweat (see Equation 6). To allow sweat to evaporate rapidly enough to maintain heat balance, the wetted area of skin must increase. The distribution of sweating may change to allow more of the skin surface area to be wetted, but wetter skin also favors development of hidromeiosis, limiting tolerance time by hampering maintenance of high sweat rates. Although heat acclimatization in a dry environment confers a substantial advantage in humid heat,[65,66] acclimatization in humid heat produces somewhat different physiological adaptations, corresponding to the characteristic physiological and biophysical challenges of humid heat.

Acquisition and Loss

A degree of heat acclimatization is produced either by heat exposure alone or by regular strenu-

ous exercise, which raises core temperature and provokes heat-loss responses. Indeed, the first summer heat wave produces enough heat acclimatization that after a few days most people notice an improvement in their feelings of energy and general well-being. However, the acclimatization response is greater if heat exposure and exercise are combined, causing a greater rise of internal temperature and more profuse sweating. Up to a point, the degree of acclimatization acquired is proportional to the daily heat stress and the amount of sweat secreted during acclimatization,[67] but full development of exercise–heat acclimatization does not require continuous heat exposure.

Continuous, daily 100-minute periods of heat exposure with exercise are widely considered sufficient to produce an optimal heat acclimatization response in dry heat. However, this notion is based chiefly on one study,[68] in which subjects' responses were evaluated only during 100-minute heat exposures, which provide little information about their ability to sustain heat-loss responses over time. An adequate assessment of heat tolerance may, in fact, require an exposure lasting several hours. For example, Strydom and Williams[69] compared responses of two groups of subjects during 4 hours of exercise in humid heat. Although the groups' responses were indistinguishable during the first hour, the responses of the more heat-tolerant group were clearly different from those of the less heat-tolerant group during the third and fourth hours.

Several factors affect the speed of development of heat acclimatization. However, most of the improvement in heart rate, skin and core temperatures, and sweat rate typically is achieved during the first week of daily exercise in a hot environment, although there is no sharp end to the improvement.[70] Heart rate shows the most rapid reduction,[71–73] most of which occurs in 4 to 5 days.[71] After 7 days, the reduction in heart rate is virtually complete and most of the improvement in skin and core temperatures has also occurred[72,74]; and the thermoregulatory improvements are generally believed to be complete after 10 to 14 days of exposure.[75] The improved sweating response[71,74] and ease of walking[72,74] reported during heat acclimatization may take 1 month to develop fully, and resistance to heatstroke may take up to 8 weeks.[76] Experimental heat acclimation (physiological adjustment to an environment, in a controlled setting) develops more quickly in warm weather,[66] probably because subjects are already partly acclimatized.

High aerobic fitness hastens development of acclimatization.[72,77] Aerobic exercise elevates core temperature and elicits sweating even in a temperate environment, and aerobic training programs involving exercise at 70% of maximal oxygen uptake ($\dot{V}O_2max$) or more[78,79] produce changes in the control of sweating similar to those produced by heat acclimatization. There has, however, been much disagreement as to whether or not aerobic training in a temperate environment induces true heat acclimatization. In a critical review of the evidence and arguments on both sides of the issue, Gisolfi and Cohen[80] concluded that exercise training programs lasting 2 months or more in a temperate environment produce substantial improvement in exercise heat tolerance. However, exercise training alone has not been shown to produce a maximal state of exercise–heat tolerance.

The benefits of acclimatization are lessened or undone by sleep loss, infection, and alcohol abuse[71,81]; salt depletion[71]; and dehydration.[71,82,83] Heat acclimatization gradually disappears without periodic heat exposure, although partial losses due to a few days' lapse are easily made up.[81] The improvement in heart rate, which develops more rapidly, also is lost more rapidly than are the thermoregulatory improvements.[68,77,84,85] However, there is much variability in how long acclimatization persists. In one study, for example, acclimatization almost completely disappeared after 17 days without heat exposure[86]; but in another study, approximately three quarters of the improvement in heart rate and rectal temperature was retained after 18 days without heat exposure.[77] Physically fit subjects retain heat acclimatization longer[65,66]; and warm weather may[66] or may not[85] favor persistence of acclimatization, although intermittent exposure to cold seems not to hasten the loss of heat acclimatization.[87]

Changes in Thermoregulatory Responses

After acclimatization, sweating during exercise starts earlier and the core temperature threshold for sweating is lowered. Acclimatization also increases the sweat glands' response to a given increment in core temperature and also their maximum sweating capacity. These latter changes reflect changes in the individual glands rather than in the nervous systems signals to the glands, because after acclimatization the glands also produce more sweat when stimulated with methacholine,[88,89] which mimics the effect of acetylcholine.

In an unacclimatized person, sweating is most profuse on the trunk; but during acclimatization in humid heat, the fraction of sweat secreted on the

limbs increases,[90–93] enabling an acclimatized person to make better use of the skin surface for evaporation and achieve higher rates of evaporative heat loss. During a heat stress lasting several hours, sweat rates that were initially high tend gradually to decline as the heat stress continues. Although several mechanisms may contribute to the decline, much of the decline is due to hidromeiosis, associated with wetness of the skin, and the decline is most pronounced in humid heat. After acclimatization to humid heat, this decline of sweat rate occurs more slowly[67] (Figure 2-15), so that higher sweat rates can be sustained and tolerance time is prolonged. This effect of acclimatization appears to act directly on the sweat glands themselves, and during acclimatization to dry heat it can be produced selectively on one arm by keeping that arm in a humid microclimate (eg, inside a plastic bag).[94]

Because heat acclimatization is an example of a set-point change,[4,95] thresholds for sweating and cutaneous vasodilation both are reduced in such a way that vasodilation and the onset of sweating accompany each other after acclimatization in the same way as before,[96] and heat transfer from core to skin is maintained at the lower levels of core and skin temperature that prevail after acclimatization. These changes by themselves say nothing about the effect of acclimatization on the levels of skin blood flow reached during exercise–heat stress. In many studies[56,97] (especially those using dry heat), heat acclimatization was found to widen the core-to-skin temperature gradient, presumably allowing heat balance to be reached with a lower level of skin blood flow and a lesser cardiovascular strain. Even in relatively dry heat, however, acclimatization to heat does not always widen the core-to-skin temperature gradient.[72]

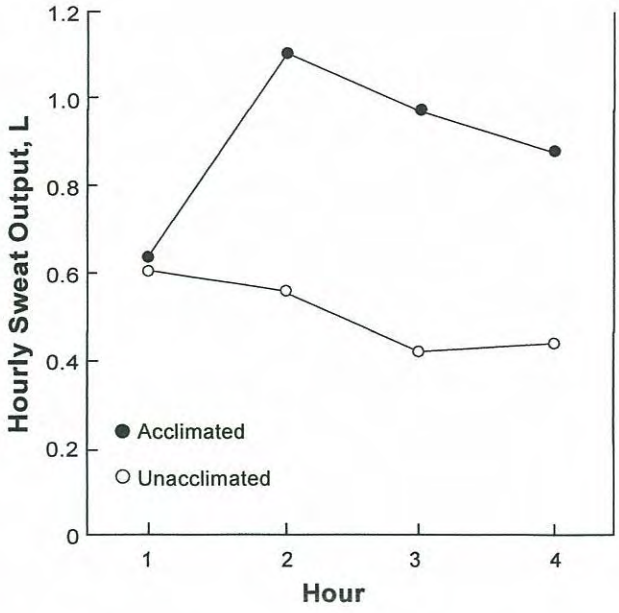

Fig. 2-15. Sweat rates during 4 hours' exercise (bench stepping, 35-W mechanical power) in humid heat (33.9°C dry bulb, 89% relative humidity, 35 mm Hg ambient vapor pressure) on the first and last days of a 2-week program of acclimatization to humid heat. Adapted with permission from Wyndham CH, Strydom NB, Morrison JF, et al. Heat reactions of Caucasians and Bantu in South Africa. *J Appl Physiol.* 1964;19:601.

Nonthermoregulatory Changes

On the first day of exercise in the heat, heart rate reaches much higher levels than in temperate conditions (see Figure 2-14), and stroke volume is lower. Thereafter, heart rate decreases and stroke volume usually, but not always, increases. Orthostatic tolerance also improves with heat acclimatization.[95] Several mechanisms participate in these changes, but their relative contributions are not known and probably vary. Plasma volume at rest expands during the first week of acclimatization and contributes to the reduction in heart rate and circulatory strain; however, if acclimatization continues, plasma volume at rest returns toward control levels after 1 or 2 weeks,[74,98–100] whereas the improvements in cardiovascular function persist. In addition, it is likely that a decrease in peripheral pooling of blood helps to support cardiovascular function in acclimatized subjects. When a decrease in skin blood flow (which is allowed by a widened core-to-skin temperature gradient) occurs, it presumably decreases peripheral pooling of blood. In addition, an increase in venous tone might substantially decrease pooling of blood, since venoconstriction can mobilize up to 25% of the blood volume.[98] The information available about such changes,[101–103] however, is very limited and far from conclusive.

Heat acclimatization increases total body water, but there is much variability both in the total increase and in its distribution among the various fluid compartments.[95] Much of the increase is accounted for by an expansion of plasma volume at rest, which develops rapidly at first and continues more slowly for about a week. The resulting increase in blood volume ranges from 12% to 27%.[104] The mechanisms responsible for this expansion are unclear, but may include an increase in extracellular fluid—ranging from 6% to 16%[104]—due to salt

retention, and a net fluid shift from interstitial space to plasma due to an increase in the mass of protein in the plasma.[105,106]

At the start of acclimatization, secretion of adrenocorticotropic hormone (ACTH) increases in response to the circulatory strain caused by heat stress. The adrenal cortex responds to ACTH by increasing secretion of cortisol and aldosterone. If salt intake is insufficient to replace losses in sweat, the resulting sodium depletion also acts via the renin–angiotensin system to increase aldosterone secretion. Cortisol and aldosterone both contribute to sodium retention: by the kidneys within a few hours, and by the sweat glands after 1 to 2 days. Exercise and heat stress also elicit secretion of aldosterone[107,108] through the renin–angiotensin system. Within a few days the sodium-conserving effects of aldosterone secreted via this pathway are sufficient to restore and maintain sodium balance, and ACTH secretion returns to normal. Depending on sodium intake, the kidneys may eventually "escape" the effects of aldosterone and excrete as much sodium as needed to maintain sodium balance. The sweat glands, however, do not escape but continue to conserve sodium as long as acclimatization persists.

An unacclimatized person may secrete sweat with a sodium concentration as high as 60 mEq/L, corresponding to 3.5 grams of NaCl per liter, and can lose large amounts of salt in the sweat (Figure 2-16). With acclimatization, the sweat glands conserve sodium by secreting sweat with a sodium concentration as low as 5 mEq/L.[27] Acclimatized men in whom sodium conservation is maximally developed can sweat up to 9 L/d and stay in salt balance on 5 grams of NaCl per day.[109,110] Maximal development of sodium-conserving capacity was accomplished with a program that combined gradual reduction of dietary sodium intake with daily exercise in the heat. However, most whites who are not secreting large volumes of sweat and are in salt balance with an intake of 10 grams of NaCl per day (a typical intake for a western diet) have high concentrations of sodium in the sweat.[111] If suddenly required to secrete large volumes of sweat, they may undergo a substantial net loss of sodium before their mechanisms for sodium conservation become fully active. Therefore, subjects who are exercising in a hot environment and are either unacclimatized or not consuming a normal diet should receive 10 grams of supplemental salt per day unless water is in short supply.[111] However, salt supplements are not recommended for acclimatized subjects performing heavy exercise in the heat if they are eating a normal diet and are not salt depleted.

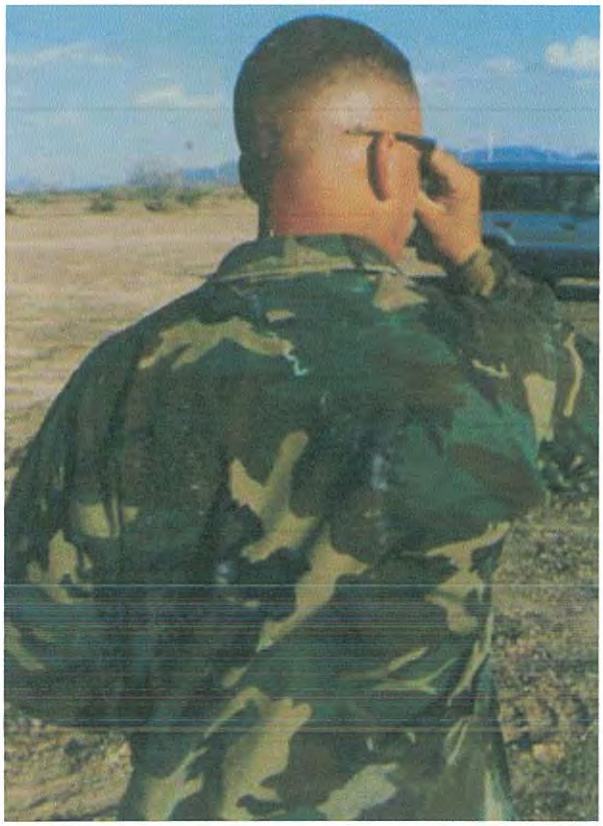

Fig. 2-16. Salt deposited on a soldier's uniform by evaporation of sweat. Photograph: Courtesy of Robert E. Burr, MD, Natick, Massachusetts.

The mineralocorticoids, aldosterone and desoxycorticosterone, have been administered to subjects just before or during heat acclimatization programs.[98,104,112,113] Mineralocorticoid administration produced some responses characteristic of heat acclimatization, but neither produced a state equivalent to what the subjects attained as a result of undergoing heat acclimatization nor reduced the time necessary to reach that state. However, because of the way these studies were designed, their results do not support definite conclusions about the role of endogenous aldosterone in heat acclimatization.[95]

Effects on Heat Disorders

The harmful effects of heat stress operate through cardiovascular strain, fluid and electrolyte loss, and, especially in heatstroke, tissue injury whose mechanism is not well understood but evidently involves more than just high tissue temperatures. The topic is also discussed in Hubbard[114] and in Chapter 5, Pathophysiology of Heatstroke, in this textbook.

Heat syncope is a temporary circulatory failure due to pooling of blood in the peripheral veins and the resulting decrease in diastolic filling of the heart. Although a large increase in thermoregulatory skin blood flow is the direct cause of the peripheral pooling, an inadequate baroreflex response is probably an important contributing factor. Heat acclimatization rapidly reduces susceptibility to heat syncope, as expected from the improvement in orthostatic tolerance,[101,115,116] noted earlier.

Like heat syncope, heat exhaustion is believed to result from a decrease in diastolic filling. However, dehydration with resulting hypovolemia has a major role in the development of heat exhaustion; the baroreflex responses usually are strong enough to prevent syncope, and also account for much of the symptomatology. Little is known about the effect of acclimatization on susceptibility to heat exhaustion.

Heatstroke is the most severe heat disorder; and without prompt, appropriate treatment, mortality may be high. Typical victims of the exertional form, in which a high rate of metabolic heat production is a primary pathogenic factor, are athletes or military personnel—especially recruits. During World War II, the incidence of fatal heatstroke was low after 8 weeks of training,[76] by which time the recruits were well acclimatized. Much of the protective effect of acclimatization is presumably owing to thermoregulatory improvement, but acclimatization and physical conditioning may also protect in ways that are poorly understood, since rectal temperatures above 41°C have been measured in runners competing in marathons with no apparent ill effect.[117,118]

A small proportion of apparently healthy individuals cannot acclimatize to heat.[119,120] In South African gold-mining recruits (the population studied most extensively in this regard) individuals who do not acclimatize are, on average, smaller, older, and less aerobically fit than those who do.[120]

Physical Fitness, Gender, and Age

Individuals with low physical fitness tend to have reduced heat tolerance and less sensitive sweating responses. Obesity also is associated with reduced heat tolerance. To a large extent, the effect of obesity is explained by its relation to physical fitness, but other factors contribute as well.[121]

Women as a group are less tolerant to exercise–heat stress than men. However, the gender difference largely disappears when subjects are matched according to size, acclimatization, and $\dot{V}O_2max$.[121] The exertional form of heatstroke is often said to be quite rare in women,[122] and perhaps women enjoy a degree of protection against exertional heatstroke for either physiological or behavioral reasons. Women are susceptible to exertional heatstroke, however, and in active-duty soldiers (a population in which most heatstroke is of the exertional type), annual incidence rates of heatstroke in women are at least half of those in men.[123] Although the thermoregulatory set point changes with the phase of the menstrual cycle, as discussed earlier, the phase of the menstrual cycle has not been shown to affect tolerance or performance during exercise in the heat (for a review, see Stephenson and Kolka[124]). It may be, however, that studies of exercise at different phases of the menstrual cycle have not used exercise of sufficient intensity or duration to demonstrate an effect. In fact, Pivarnik and associates,[125] studying women's responses during exercise in a temperate environment (22°C), found that after 60 minutes of exercise heart rate was 10 beats per minute higher in the luteal phase than in the follicular; and that rectal temperature increased 1.2 Centigrade degrees in the luteal phase and was still rising, while it increased 0.9 Centigrade degrees in the follicular phase and was near steady state. Although they examined only one set of experimental conditions, their data, when extrapolated to warmer environments, suggest a decline in tolerance to exercise–heat stress during the luteal phase. Advancing age also is associated with a decline in heat tolerance. Most of the decline disappears, however, if effects of chronic disease, adiposity, and reduced physical fitness are eliminated.[126]

Drugs and Disease

Many drugs inhibit sweating, most prominently those used for their anticholinergic effects, such as atropine and scopolamine. Intramuscular injection of 2 mg atropine (the dose in one autoinjector for acute treatment of exposure to nerve agent) inhibits sweating sufficiently to cause a noticeable impairment of thermoregulation during walking in dry heat.[127] Some drugs used for other purposes, such as glutethimide (a sleep medicine), tricyclic antidepressants, and phenothiazines (tranquilizers and antipsychotic drugs) also have some anticholinergic action; and all of these, plus several others, have been associated with heatstroke.[128,129] A 30-mg oral dose of pyridostigmine bromide (the dose